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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/916,140	08/21/97	SCOTT M	SUV-003.04

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EXAMINER	
SCHNIZER, R	
ART UNIT	**PAPER NUMBER**
1632	18

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	08/916,140	SCOTT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 11/6/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/916,140 is acceptable and a CPA has been established. An action on the CPA follows.

A preliminary amendment was received and entered as Paper No. 17 on 11/6/00. All previously pending claims were canceled, and new claims 61-73 were added as requested. Claims 61-73 are pending and under consideration in this office action.

Claim Objections

Claims 61 and 63-73 are objected to because of the following informalities: In line 4 of claim 61, the words "patched inhibited" should be joined by a hyphen. In line 13 of claim 63, the word "constructs" should be singular, not plural. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claim 62, 72, and 73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 62, 72 and 73 are drawn to methods wherein agents are added to a cell having a patched loss of function phenotype in order to identify agents which reverse the patched loss of function phenotype. There appears to be no support for this assay in the specification. It is noted that the specification discloses at page 20, lines 28 and 29, an assay in which agents are added to a cell which lacks functional patched, and the ability to reproduce functional patched is then assayed. This differs from the claimed invention in at least two ways. First, the claim recites a cell with a patched loss of function phenotype, whereas the specification discloses a cell with a loss of patched function. Because patched is part of a signaling pathway, it is reasonable to assume that mutations in other pathway proteins can interfere with the ability of patched to exert its function, and would therefore cause a patched loss of function phenotype. The specification does not appear to contemplate the use in the claimed method of cells comprising such mutations, yet these cells are encompassed by the claim. Second, the specification discloses a method in which the agents stimulate the production of patched in a cell which lacks functional patched, whereas the claim requires a reversal of the patched loss of function phenotype. Again, because patched participates in a pathway, it is reasonable to expect that one might be able to reverse the

loss of function phenotype by stimulating the pathway at a point downstream of patched. However there appears to be no literal support for this method in the specification as filed.

Enablement

Claims 61-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of identifying agents which affect patched-dependent signal transduction, does not reasonably provide enablement for methods of identifying agents which are useful for treating an animal having a disorder characterized by a loss of function of a patched gene or which inhibit the growth of cells *in vivo* or *in vitro*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 61-71 are directed to methods of identifying agents which can be used to treat an animal having a disorder characterized by a loss of function in a patched gene. It is noted that the claims are not directed to prevention of disorders, rather they are directed to treatment of existing disorders. Claims 72 and 73 are directed to a method of preparing agents which inhibit the growth of cells *in vivo* or *in vitro*. The central issue in the analysis of enablement of these claims is whether agents identified *in vitro* by the claimed methods will be useful in treating disorders *in vivo*. With respect to claims 72 and 73, the issue of whether or not the method will develop agents which inhibit cell growth is considered.

The prior art and the specification provide substantial evidence that patched is a tumor suppressor, and that loss of patched function can lead to tumor formation. In particular, the patched gene had been identified as a locus involved in basal cell nevus syndrome, which frequently leads to basal cell carcinoma (BCC). Other phenotypes asserted to be associated with a loss of patched function, and which are encompassed by the claims as treatable conditions, include aberrant development of cells, tissues, or organs with respect to size, symmetry, or functional performance, specifically including polydactyly, syndactyly, craniofacial alterations, and spina bifida. See the specification at page 2, lines 22-27, and page 7, lines 3-6.

At the time of the invention, the issue of whether or not pharmacological agents which mimic the effect of patched could be used to treat basal cell carcinoma (BCC) was not settled. Gailani et al (J. Nat. Canc. Inst. (1997) 89(15):1103-1109) taught that "[f]urther studies into the function of patched and other interacting genes **may suggest** alternative methods for the treatment and prevention of BCCs. Pharmacological agents that mimic the effect of patched **may form the basis** for a topical medical treatment that would serve as an alternative to surgery. **If patched truly acts as a gatekeeper gene**, similar agents could be used in prevention of BCCs in susceptible individuals." Emphasis added. These statements reflect the highly unpredictable nature of the physiological art in general, and more specifically, the need for further research in order to establish whether or not it is even possible to inhibit cell growth through the administration of agents intended to mimic the effect of patched. The assays recited in the method steps of the instant invention represent the first steps in this research. However, the

selection of agents to be tested in the method is problematic because the biochemical role of patched in cancer was not well understood at the time of the invention. See Pennisi, Science 272:1583-1584, especially last sentence on page 1583. This necessitates further research before potential cancer therapy targets can even be selected. See Pennisi, page 1584, column 3, last two paragraphs. Guidance in the specification as to the selection of agents to test is limited to the definition of agents as "preferably small organic compounds having a molecular weight of more than 50 and less than 2,500 Daltons", and a non-limiting exemplary list of classes of molecules including peptides saccharides, fatty acids, steroids, purines, and pyrimidines. See page 19, lines 22-31.

Even if the claimed methods could be used to successfully identify agents that mimic the effect of patched *in vitro*, and which inhibit cell growth, the development of such agents into drugs which can be used *in vivo* is highly unpredictable. It is well established in the art that drugs which are discovered by *in vitro* assays are not necessarily useful for *in vivo* applications. A variety of issues must be contemplated in moving from *in vitro* to *in vivo* applications, including bioavailability of the drug, toxicity of the drug, pharmacokinetics, drug metabolism and clearance, and potential drug interactions. Furthermore, factors such as the age, health, sex, and species of the patient may also affect the metabolism and performance of the drug in unpredictable ways. See Kato (Nippon Yakurigaku Zasshi. Folia Pharmacoligica Japonica (102(3): 245-252, 9/1993.)

The use of the invention to produce agents useful in treating gross physical abnormalities is discussed below. Polydactyly is a developmental disorder resulting in excess fingers or toes. It

seems unlikely that administration of any agent to a polydactylous adult could reverse the developmental process which resulted in the formation of bones, muscle, connective tissue, and vasculature which constitute an extra digit. The same can be said for any other developmental disorder which results in a gross physical abnormality such as an increase in the size of the skull or facial features. There is no precedent for any drug which can be administered to an individual to reverse physical effects of spina bifida such as the protrusion of the spinal cord and meninges, or a cleft spine. On the contrary, treatment of such developmental disorders is generally preventive in nature, and is not practical after the physical malformation is apparent. For example, folic acid is given to mothers during pregnancy in order to avoid spina bifida, however, there are no reports of the treatment of spina bifida by administration of folic acid after physical manifestation of the defect.

To summarize, it was unknown at the time of the invention whether or not the claimed methods could successfully identify compounds which could inhibit cell growth; further experimentation is required to identify potential agents for testing because the biochemical role of patched in proliferative disease is unclear, and because the specification fails to provide adequate guidance in this regard; the predictability of successfully developing a useful *in vivo* drug from an *in vitro* assay is extremely low due to the unpredictable factors associated with *in vivo* metabolism of drugs; and there is no precedent for the drug-induced reversal of a gross physical abnormality such as polydactyly, and the prospect of developing such successful treatments seems extremely low. For these reasons, one of skill in the art could not use the claimed methods to produce

agents useful for treating patched loss of function disorders *in vivo* without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62, 72, and 73 are indefinite because it is unclear what constitutes a partial reversal of a patched loss of function phenotype in an isolated cell. First, the specification fails to define this phenotype in the context of an isolated cell, so it is unclear precisely what constitutes a phenotype. Second, even if the phenotype were defined, the specification fails to provide any standard for determining what constitutes a reversal "at least in part" of the phenotype. Similarly the specification fails to define what constitutes "a portion of the patched loss of function phenotype" because the phenotype itself is not disclosed, and it is unclear what is intended by "a portion" of a phenotype.

Claims 63-71 are indefinite because it is unclear what is expressed in the second recombinant cell. It is suggested that the words "reporter gene" should be inserted prior to the word "expression in line 5 of claim 63, and prior to the word "transcription" in line 8 of claim 63. .that the wordtranscript and product should be measured in the second recombinant cell. Also, at line 12 of claim 63, it is unclear what is intended by "a functional wild type patched". Specifically it is unclear whether the term "patched" refers to a gene, an RNA or a protein.

Claim 64 is indefinite because it recites "comparing the difference" without antecedent basis. Claim 64 is dependent on claim 63 in which "amounts" are compared, and a difference is determined. The difference is not compared to anything.

Claim 71 is indefinite because "the cell having a patched loss of function phenotype" is recited without antecedent basis. Claim 71 depends from claim 63 which recites a cell that does not express a functional wild type patched, but does not recite the phenotype of the cell.

Claims 72 and 73 are indefinite because the recited method steps are not concordant with the purpose set forth in the preamble. Specifically, there is no step which requires the inhibition of the growth of cells. Furthermore claim 72 contains the sentence fragment, "preparing a formulation including a test agent selected in step (b) and a pharmaceutically acceptable diluent" repeated at the end of the claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

Karen M. Hauda

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